REMARKS

The Applicants appreciate the Examiner's thorough examination of the subject application. Applicants request reconsideration of the subject application based on the following remarks.

As an initial matter, Applicants appreciate the courtesy extended by Examiner Fubara during a telephonic interview conducted on May 25, 2005. During the interview, means of presenting evidence of unexpected or superior results which would be sufficient to overcome the pending 103(a) rejections were discussed.

Claims 1-20, 37-42, and 52-53 are currently pending in the application, of which claims 12 and 13, have been withdrawn from consideration. Claims 21-36 and 43-51 have been cancelled in this or a previous amendment without prejudice or disclaimer to Applicants right to pursue the subject matter of the cancelled claims in this or a subsequent application. Support for the amendments to the claims can be found in the specification. No new matter has been added by the amendments to the specification or the claims.

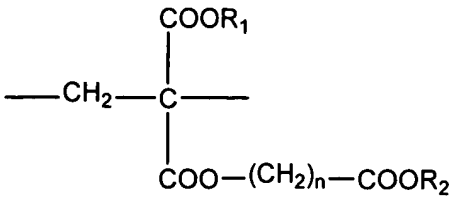
As the office action is understood, the sole remaining grounds for rejection of the claims is presented in paragraphs 4 and 5 of the final office action dated June 15, 2004.

Thus, Claims 1-11, 14-20, 37-42, 52, and 53 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Bru-Magniez et al. (U.S. Patent 6,211, 273).

The rejection is traversed.

Claim 1, as amended, provides pharmaceutical compositions comprising microparticles having a mean particle size of between 1.0 μm and about 100 μm, wherein the microparticle comprises a polymeric support material in which a substance can be dispersed, wherein the

support material comprises at least about 50% w/w of at least one homopolymer with a repeat unit according to Formula (I):



wherein

R_1 represents a C_1-C_6 alkyl group or a group $(CH_2)_m$-$COOR_3$ wherein m is an integer from 1 to 5 and R_3 is a C_1-C_6 alkyl group, R_1 and R_3 being the same or different;

R_2 represents a C_1-C_6 alkyl group the same or different from R_1 and R_3;

n is an integer from 1 to 5; and

at least one therapeutic agent that is encapsulated or dispersed in the polymeric support material of the microparticle.

Claim 37, as amended, provides methods of treating a urological disease or disorder comprising:

administering intravesically a microparticle having a mean particle size of between about 1.0 μm and 100 μm with one or more encapsulated therapeutic agents to the lumen of the bladder;

contacting the particles to the surface of the mucosa,

releasing the encapsulated therapeutic agent in a controlled manner to treat the urological disease or disorder.

In contrast, Bru-Magniez teaches nanoparticles having a particle size of less than 500 nm and methods of making nanoparticles having a particle size of less than 500 nm, which nanoparticles are composed of a therapeutic agent and a methylidene malonate polymer.

As the Bru-Magniez patent is understood, nanoparticles having a mean particle size of greater than 500 nm are neither disclosed nor suggested. Moreover, methods of preparing

particles having a mean particle size of greater than 500 nm are neither disclosed nor suggested by Bru-Magniez.

In contrast, Applicants have surprisingly discovered that larger microparticles (e.g., particles with a mean particle size of between 1-100 μm) are retained in the bladder of a patient after intravesical administration. That is, Applicants have surprisingly discovered that larger microparticles remain in the bladder after administration without being discharged in the urine stream and without being transported from the bladder to other organs or tissues.

Applicants have further discovered in connection with particles composed of poly(phosphoester) poly(D,L-lactide-*co*-ethyl phosphate), which is referred to herein as "P(DAPG-EOP)", that microparticles and nanoparticles behave differently upon administration to the bladder. As recited by Experiment 4.1-4.6 of the attached Rule 1.132 Declaration, Dr. Leong has discovered that nanoparticles, having a mean particle size of 600 nm and composed of P(DAPG-EOP) and a DNA molecule, are transported to the lymph nodes shortly after intravesical administration in the bladder. In contrast, compositionally identical microparticles, having a mean particle size of about 5 μm, are retained in the bladder without transport to the lymph nodes. Thus, microparticles, which are retained by the bladder, are particularly suitable for the delivery of therapeutics in the treatment or prevention of urological disorder.

Dr. Leong, in the enclosed Declaration, has affirmed that the size-dependent retention of particles in the bladder observed for the P(DAPG-EOP) particles will likely also occur for PMM 2.1.2 particles. As indicated in the Declaration, Dr. Leong has based this statement on his extensive personal experience in the field of polymeric drug delivery systems. Thus, Dr. Leong concludes based on (1) the retention in the bladder of microparticles having a 2-5 μm diameter for both PPM 2.1.2. and P(DAPG-EOP) and (2) the observed transport of the nanoparticles (600 nm mean size) of P(DAPG-EOP) from the bladder to the lymph nodes, that nanoparticles composed of PPM 2.1.2. which have a mean particle size of less than 500 nm will likely also be

transported from the bladder to other tissues or organs of the patient after intrabladder administration.

Consequently, the claimed pharmaceutical compositions of claim 1, which comprise microparticles having an average particle size of between 1 and 100 μm would not have been obvious to one of ordinary skill in the art.

The Bru-Magniez patent does not teach or suggest the use of any nanoparticle for the treatment of a urological disease or disorder. Moreover, Bru-Magniez does not teach or suggest any method of treatment comprising delivery of a particulate material to the bladder or more particularly, methods of treating urological diseases or disorders (including cancer) in which microparticles having a mean particle size of between 1.0 and 100μm are administered to the lumen of a patient's bladder.

Claim 37, which provides methods of treating urological diseases and disorders with microspheres having a mean particle size of 1-100 μm, also would not have been obvious to one of ordinary skill in the art based on the disclosure of Bru-Magniez. As noted above, the larger particles provide improved retention in the bladder. Moreover, Bru-Magniez neither discloses nor suggests administration of nanoparticles to the bladder or the use of said nanoparticles in the treatment of urological diseases or disorders.

Thus, one of ordinary skill in the art would not have been motivated to practice the instant invention based on the teachings or suggestions of the Bru-Magniez patent.

Applicants respectfully submit that claims 1 and 37 are patentable over the Bru-Magniez patent. Claims 2-20, 38-42, and 52-53 depend from claim 1 or claim 37 and are therefore also patentable over Bru-Magniez.

Early consideration and allowance of the application are earnestly solicited.

Respectfully submitted,

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